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Nutritional Interventions to Improve Symptoms of Attention Deficit Hyperactivity Disorder

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**Nutritional Interventions to Improve Symptoms of Attention Deficit
Hyperactivity Disorder**

by

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A Starred Paper

Submitted to the Graduate Faculty of

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Chapter 1: Introduction

“The doctor of the future will no longer treat the human frame with drugs, but rather will cure and prevent disease with nutrition.” ~Thomas Edison

“Let food be thy medicine and medicine be thy food.” ~Hippocrates

Attention Deficit Hyperactivity Disorder (ADHD) is one of the most common behavioral disorders in childhood that continues into adulthood (Pelsser, Frankena, Toorman, Savelkoul, Pereira, & Buitelaar, 2009). It is estimated that 1 in 10, or 11%, of children aged 5-17 are diagnosed with ADHD (Visser, Holbrook, Danielson, Bitsklo, & Zablotsky, 2015). Most children are diagnosed by age 7, but prevalence of ADHD is higher among older children. Boys are twice as likely to be diagnosed as girls, and non-Hispanic white children are diagnosed more often at ages 12-17 than children of other races. The prevalence of ADHD is higher among children whose families have public insurance (Pastor, Reuben, Duran, & Hawkins, & Center for Disease Control, 2015). Long-term risk outcomes of children with ADHD include underachievement at school, antisocial personality disorder, delinquency, substance abuse, relationship breakdowns, and unemployment (Pelsser et al., 2009). Current professional recommendations to treat ADHD include medications and psychosocial interventions (Pelsser et al., 2009). These interventions are commonly used because they are easily accessible.

The treatment of ADHD should not be a one size fits all approach and prescriptions such as Adderall, Ritalin, and Concerta can carry high price tags and serious warnings. The use of prescription drugs to treat ADHD can cost a family between \$15 a month to \$300 per month, depending on brand and dosage. Liquid formulations of the medication can cost as much as \$500 per month (Consumer Reports Best Buy Drugs, 2012). Another concern with treating ADHD with prescription drugs is the potential for negative side effects such as: reduced appetite,

weight loss, change in personality, sudden death, heart attacks, and hallucinations. Parents and some practitioners have been looking for alternative treatments (Parker-Pope, 2008).

Studies have investigated links between ADHD and nutrition, more specifically whether it could be caused by a sensitivity or allergy to additives such as food colorings and preservatives, whole foods such as dairy, soy, gluten, eggs, or grains, or a deficit of a specific nutrient such as zinc, iron, or B12. Much of the current United States population consumes a diet that can be referred to as a Western Pattern Diet, or Standard American Diet (SAD). The Western pattern and the SAD diet consist primarily of high intakes of refined and processed foods, alcohol, salt, red meats, sugary beverages, snacks, eggs, and butter. Consuming foods typically low in potassium and high in sodium, fats, and simple carbohydrates has been implicated in many diseases including atherosclerosis, type II diabetes, hypertension, and obesity as well as Learning Disorders.

This paper focuses on how nutrition can affect the ability to learn and contribute to ADHD. It also investigates effective nutritional options which have been tested and demonstrated positive results for treating symptoms of ADHD. This paper reviews findings from the additive-free diet, few foods elimination diet, and supplementing nutritional deficits.

Research Question

1. What nutritional interventions have been investigated for children and youth to treat ADHD?
2. How effective are nutritional interventions for treating ADHD?

Focus of Review

The review of literature and studies in Chapter 2 include studies with participants who are identified as having ADHD with exception to the two food additive studies. My initial focus was to investigate alternative treatment options for treating ADHD. This focus was broad and resulted in a broad range of options. I chose to narrow my focus on nutrition, more specifically on restrictive/elimination diets, and supplementation for treating ADHD. I chose to focus even further to include studies on children not currently taking prescription medications for ADHD except for one Omega-3 study.

The Academic Search Premier database and was used to locate studies, articles, and books using a variety of keywords and keyword combinations, including the following: *ADHD, Attention Deficit Hyperactivity Disorder, diet, restriction diet, Feingold diet, alternative treatment, food additives, food sensitivities, gluten free, supplementation, magnesium, iron, red ginseng, food colorings, zinc, fatty acids, omega-3, EPA, DHA, L-theanine*. I also searched the internet for definitions and statistics regarding ADHD, ADHD prescription cost, and Western Pattern and SAD diets.

Importance of Topic

Recent studies confirm the influence of diet and nutrition on behavior and learning in children and adolescents, particularly with respect to fatty acid supplements and food reactions.

As a parent of a child who demonstrates some tendencies of ADHD and as a special education teacher, I have come to question what, aside from prescription drugs, can help my child or my students focus better in school. Multiple parents report negative side effects of their child's prescription and have a difficult time enforcing them to take it.

Studies suggest that ADHD symptoms could be the result of or triggered by certain food additives, sensitivities, allergies, or deficits. It is important to explore what foods or deficits might contribute to symptoms and what interventions might be helpful in reducing symptoms of ADHD.

Chapter 2: Review of Literature

Twelve quantitative research studies that investigate nutritional supplements to reduce symptoms of ADHD and the association between foods and additives and symptoms of ADHD in students are included in the Chapter 2. Tables 1, 2, and 3 summarize the findings of these studies and categorize them by the types of interventions assessed and in chronological order.

Dietary Supplements

Vitamins, minerals, and herbs have been studied as a means to improve overall nutrition as well as deficits for children and youth with ADHD. Six studies of supplements are included in this section: two on minerals, two on fatty acids, and two herbal.

Bilici et al. (2004) investigated zinc sulfate in the treatment of ADHD. The authors hypothesize that zinc administration would lead to significantly reduced ADHD symptoms compared to a placebo, as measured by the *Attention Deficit Hyperactivity Disorder Scale* (ADHDS), *Turkish Adaptation of Conners Teacher Questionnaire* (TACTQ), and *DuPaul Parent Ratings of ADHD* (DuPaul).

The study consisted of 400 children (72 girls, 328 boys) between the ages of 6 and 14 in the first five grades that met the criteria for DSM-IV diagnosis for ADHD by psychiatric evaluation. Exclusions included another axis I disorder, comorbid illness, and any other medical conditions. Participants were randomly assigned to a 1:1 ratio to receive oral zinc sulfate (n=202) or placebo (n=198) for a 12-week, double-blind treatment phase. A fixed-dose (150-mg) of zinc sulfate and a placebo (sucrose, 150 mg) were orally administered for a period of 12 weeks by mixing it in a breakfast drink. The dose was kept fixed throughout the duration

of the study. Participants were evaluated to develop a baseline, and then evaluated after week 1, week 4, and week 12.

The ADHDS, conducted by clinicians, consists of 46 questions that were administered at baseline, on week 1, week 4, and week 12 and consists of four subscales: 1) Attention Deficit, 2) Hyperactivity, 3) Impulsivity, and 4) Impaired Socialization Subscales. The TACTQ consists of three subscales: 1) Attention Deficit, 2) Hyperactivity, and 3) Conduct. The DuPaul is a 14-item scale that is different for females and males. The Connors and DuPaul scales were administered twice at the beginning of the study and again at week 12.

Biochemical and hematological tests were completed twice at baseline and after week 12. Each of the participants had to undergo a 12-h fast before a blood sample was collected to measure the fatty acids and zinc levels. Serum Zinc levels were measured using the atomic absorption spectrometry (AAS). Free fatty acids (FFA) levels were determined using the colorimetric and enzymatic method and by using the Wako commercial kit.

The Pearson correlation, chi-square, and t test were applied to clinical and laboratory safety data for each within-group parameter. The data gathered from all 400 participants were used in assessing the safety of zinc supplementation and data from 95 participants in the zinc group and 98 from the placebo group was used to assess efficacy. At week 12 the zinc group had increased levels of zinc compared to baseline ($t=12.7$, $df=96$, $p=.01$) and FFA when compared to baseline ($t=4.1$, $df=55$, $p=.03$). The Pearson correlation showed no connection between BMI or age and the ADHDS scores.

ANCOVA was used to assess the primary and secondary efficacy analyses of the differences from baseline to endpoint in mean ADHDS and TACTQ scores between the zinc and

placebo groups. The difference between the zinc group and the placebo group was significant ($F=11.7$, $df=1,191$, $p=.002$) and was evident at week 4 and maintained through week 12. The mean score of the TACTQ-Hyperactivity subscale was reduced from baseline for the zinc group and for the placebo group ($F=7.2$, $df=1,187$, $p=.03$) and the score of the TACTQ-Conduct subscale was reduced from baseline for the zinc group and by for the placebo group ($F=5.2$, $df=1,187$, $p=.04$). It was noted the change in mean scores of the TACTQ-Attention Deficit subscale and the DuPaul between the two groups were not significantly different.

On week 4, participants of the zinc group had significant improvement with hyperactivity, impulsivity, and impaired socialization symptoms of ADHD when compared with the placebo-group; however, there was no positive effect on attention deficit score. The zinc and placebo supplements were both well tolerated by the participants with ADHD. A metallic taste in the mouth was the most frequent complaint for both the zinc supplement and placebo groups. Limitations noted of this study include: maintenance of the fixed zinc doses, the short duration of the treatment, and the lack of a control group to take a stimulant drug, amphetamine.

Konofal et al. (2008) carried out a double-blind, placebo-controlled, randomized pilot trial of the effects of iron supplementation on attention deficit hyperactivity disorder in children. Iron deficiency has been suggested a possible contributing cause of ADHD in children.

Twenty-three outpatient non-anemic children aged 5-8 years with serum ferritin levels <30 ng/mL who met DSM-IV criteria for ADHD and had normal hemoglobin levels were selected for the 12-week trial. Subjects were excluded if they had an $IQ < 80$ by the French version of the *Wechsler Intelligence Scale*, third edition for children, relevant psychiatric comorbidities (depressive, anxiety, and sleep disorders per DSM-IV criteria), or chronic medical

conditions (including malnutrition). Children were also excluded who had been taking an iron supplement in the past 3 months or previous treatment with psychotropic agents or psychostimulants.

The subjects who satisfied all the entry criteria were randomized to a ratio of 3:1 in blocks of four patients, to either oral iron (ferrous sulfate tablets, 80 mg/day, n=18) or placebo tablets (n=5) once daily in the morning for 12 weeks. The ratio of 3:1 was chosen for ethical reasons, being that the selected children had documented iron deficiency. The study consisted of five visits; screening, baseline, and at weeks 4, 8, and 12. Iron measures were based on several measures of biochemical and hematological variables, including serum iron, ferritin, transferrin, and soluble transferrin receptors. Investigators were kept blinded after the screening.

The primary outcome measure was the *Conners' Parent Rating Scale* (CPRS) which is a questionnaire measuring symptoms on a 0-3 scale. To measure the secondary outcome, the *Attention Deficit Hyperactivity Disorder Rating Scale* (ADHD-RS), *Conners' Teacher Rating Scale* (CTRS), *Clinical Global Impression-Severity* (CGI-S), and iron status measured at baseline, and after 4, 8, and 12 weeks of treatment. At the end of the 12 weeks, the *Clinical Global Impression-Improvement* (CGI-I) subscale score was measured. Patients, parents, teachers, and investigators were completely blind to treatment and to biochemical measures during the trial.

The correlations between serum ferritin levels and ADHD-RS scores were produced using Pearson correlation coefficients. The changes from baseline to weeks 4, 8, and 12 were analyzed using parametric (paired Student's test) or nonparametric (paired Wilcoxon test) methods when appropriate for both groups. Serum ferritin levels increased in the iron treatment

group at baseline to week 12 ($p=0.000$) and levels in the placebo group remained unchanged throughout the study. More improvement was shown in the CPRS in the iron group ($p=0.055$) than the placebo group ($p=0.769$) and ADHD-RS scores were significantly reduced after 12 weeks in the treatment group ($p=0.008$), but not the placebo group ($p=0.308$). Similarly, an improvement was shown on the CTRS for the treatment group ($p=0.076$ for within-group change) but not in the placebo group.

In this study, subjects that participated in the treatment group showed significant improvement on the total score of the ADHD-RS as well as on the hyperactivity/impulsive and inattentive subscales. The effect size of the difference between the treatment group and the placebo group on the ADHD-RS was large (Cohen's $d=0.81$). CGI-severity and improvement scores were also significantly improved in the treatment group but not the placebo group. The CGI-I was not significant between groups. The iron supplementation was well tolerated by the subjects. Adverse effects reported were: abdominal pain (2 of the 18) and constipation and vomiting (1 of the 18). In the placebo group, abdominal pain was reported in two of the five. Limitations of the trial are the small sample size, especially of the placebo group.

Gustafsson et al. (2010) investigated whether eicosapentaenoic acid (EPA) supplementation improves teacher-rated behavior and oppositional symptoms in children with ADHD randomized, double-blind study.

Children aged 7-12 years of age that meet the DSM-IV criteria for ADHD-combined type with any neuropsychiatric co-morbidity were eligible. Exclusions for the study include: IQ<70, autism, major depression, epileptic seizure within last 2 years, other neurological disorder, endocrinological disorders, fish allergy, severely impaired hearing and vision, severe sleeping

disorder, psychotic symptoms or other ongoing medication. No child had been on stimulants and if they were taking a long chain polyunsaturated fatty acid (LCPUFA) supplement they did a wash-out period of 10 weeks prior to the study. Eighty-two children were included in the 15-week study. They were randomized to four groups to receive either one capsule daily orally of PlusEPA or placebo in a 1:1 ratio. PlusEPA contains 500 mg EPA + 2.7 mg Docosahexaenoic acid (DHA) and 10 mg Vitamin E mixed tocopherols. The placebo was a combination of rapeseed oil and medium-chain triglycerides (<10% of PlusEPA content of omega-3 LCPUFA) in a capsule identical to the PlusEPA capsule.

Outcome measures were assessed by parents and teachers using the *Conners' Rating Scale* (CPRS and CTRS) evaluating three clinical domains: hyperactivity-impulsivity, inattention/cognitive problems, and oppositionality. A doctor and study nurse administered the following psychological tests: ADHD-RS to confirm ADHD diagnosis, *Raven's Progressive Matrices* to assess nonverbal reasoning, and Qb-test to measure hyperactivity. Blood samples were collected to measure PUFA and parents filled out a food frequency questionnaire so that the intake of daily energy and fat could be calculated.

Between-groups comparison was based on the within-subject CPRS + CTRS scores from baseline to endpoint analysis was the primary measure. Mann-Whitney or chi-square were used due to distributions not being normal. Fatty acid was analyzed using a t-test, Kedall's Tau was used to measure correlation and regression. All comparisons used two-sided statistical tests at the 5% significance level. Bonferroni adjustment for multiple comparisons was performed for CPRS and CTRS.

On the CPRS and the CTRS, primary efficacy findings variables were essentially negative. Results of the treatment group and the placebo group were found to be similar. However, on the CTRS subscale for inattention/cognitive difficulties significant improvement was seen in the treatment group. Due to limited results, a series of post-hoc analysis was performed. Oppositional problems were found to have significantly improved (ES 0.63, $p=0.026$). The treatment group had a mean improvement score of 12 whereas the placebo group had a mean improvement score of 1.5 (ES 0.63, $p=0.01$). Oppositional behavior and inattention/cognitive problems showed significant improvement but not in hyperactivity for the oppositional subgroup, $\geq 25\%$ improvement was seen in 52% receiving EPA vs 9% for placebo ($p=0.001$). The difference in the hyperactivity/impulsivity on the Qb-test was not significant between the groups ($p=0.177$). All of the children demonstrated less hyperactivity/impulsivity and oppositional behavior.

PUFA levels found in serum of both the placebo and treatment group were similar at baseline and children who received the PlusEPA showed a 159% increase in their EPA concentration and 160% increase in their red blood cell (RBC) at 15 weeks. PUFA levels remained unchanged or decreased in the placebo group.

The double-blind RCT study, two subgroups of children with ADHD characterized by oppositional behavior and less hyperactivity/impulsivity, demonstrated a significant reduction in symptoms in the supplementation with EPA group; however, it did not eradicate core hyperactivity symptoms. Improvements were found in inattention/cognitive on the CTRS based on behavior in the classroom. It was found that children that responded to the treatment had lower levels of EPA and higher levels of omega-6 at baseline. Increasing the EPA levels and

decreasing the omega-6 levels were related to clinical improvement after 15 weeks of treatment. Limitations of the study include: patient selection could be biased as parents that agreed to participate might have a more positive interest in alternative treatment and might rate improvement unconsciously, an oil with less omega-6/omega-3 might give greater difference between treatment and placebo, subgroups were not defined prior to the study but constructed in post-hoc analysis, low number of girls participated, dosing was at a low level. No adverse side effects were reported and is considered safe.

Lee, Lim, and Park (2011) investigated the clinical effects of Korean red ginseng (KRG) on attention deficit hyperactivity disorder in children. Eighteen male subjects aged 6-14 that met the DSM-IV criteria for ADHD, had history of psychiatric drug administration, and had visited the Dankook University Hospital from August to September, 2010, were selected to participate in a single arm open case study for 8 weeks.

On the first visit, participants of the study were given a physical examination and basic history was evaluated on the first visit and a child psychiatrist performed the clinical scales: *Korean version of Child Behavior Checklist (K-CBCL)*, *Korean Personality Inventory for Children (KPI-C)*, *Kovac's Children's Depression Inventory (CDI)*, *Spielberger State Anxiety Inventory (SAIC)*, and *Spielberger Trait Anxiety Inventory (TAIC)* as well as the *ADHD Diagnostic System (ADS)*. Parents completed the *Abbreviated Conners Parent-Teacher Rating Scale-Revised (CPRS and CTRS)* and the *Korean version of DuPaul Attention Deficit Hyperactivity Disorder Rating Scales (K-ARS)*. The same clinical assessments were administered on the first visit and repeated at each visit. On the second visit, participants began

the KRG therapy supplied in tablet form containing 500mg of KRG extract to be administered half a tablet twice daily.

Repeated measures t-test was performed to compare results before the KRG medicine and at weeks 1, 4, and 8 weeks after administration. Therapeutic effects reported for ADHD symptoms observed through ADS, a significant difference was found in omission error ($F=6.3$, $p=0.023$) (omission error measures inattention), the Conners ADHD scale showed a significant difference in the score ($F=4.89$, $p=0.042$), the K-CBCL a significant score was not found in all subscales, the KPI-C a significant score reduction was found in the physical development scale ($F=7.07$, $p=0.017$) and social relations scale ($F=6.15$, $p=0.025$). The only adverse effect reported by participants was the bad taste. Limitations of the study include: small sample size without controls, the clinical responses to KRG found cannot be generalized for the entire ADHD population.

Ko et al. (2014) investigated the effects of Korean red ginseng (KRG) extract on behavior in children with symptoms of inattention and hyperactivity/impulsivity. There is evidence that KRG can reduce the production of the adrenal corticosteroids, cortisol, and dehydroepiandrosterone (DHEA), and thus may be a viable treatment option for ADHD. A single-center, double-blind, randomized, placebo-controlled trial was performed in a tertiary care academic hospital in Daegu, Korea, to evaluate whether red ginseng treatment improved attentiveness and adrenal function in children with chronic stress. Seventy-two children met the inclusion criteria of being aged 6-15, having more than six symptoms of inattention or hyperactivity/impulsivity that are diagnostic criteria for ADHD DSM-IV. Exclusion criteria of taking drugs that could affect psychological symptoms limited the number patients so the study

was opened to include ADHD-NOS (not otherwise specified). All patients had symptoms for more than 6 months and had morning salivary cortisol levels less than 10 ng/mL, which is considered to indicate chronic stress. Exclusions applied if the subjects were taking drugs that could affect psychological symptoms, including antipsychotic drugs; common cold drugs such as amphetamine, ephedrine, and ginseng products; or vitamin supplements. Subjects were also excluded if they had adrenal or thyroid disease, or if they had a psychological diagnosis with the preceding 3 months. The subjects were assigned randomly 1:1 to KRG treatment group (n=35) or control group (n=37). During the study, saliva samples were not collected for two subjects in the KRG group so they were excluded. The final study population consisted of 70 subjects KRG group (n=33) and control group (n=37).

A 2-week screening period allowed analysis of demographic data, past medical history, medication use, and vital signs of each subject. Following week 2, they were randomly assigned in a double blind manner to receive one pouch (40 mL) of KRG extract twice a day or one pouch (40 mL) of an identically flavored and packaged placebo twice a day. All participants, care providers, and those assessing were blinded after assignment to interventions. The study duration was 8 weeks with evaluations at baseline, 4 weeks, and 8 weeks after treatment assignment. Subjects were assessed using 18 questions pertaining to DSM-IV diagnostic criteria and parents and/or teacher completed a questionnaire to assess the subject's symptoms of inattention or hyperactivity/impulsivity, and *Quantitative Electroencephalography Theta/Beta Ratio* (QEEG-TBR) was performed.

The KRG treatment group and the control group were compared in terms of baseline characteristics by using Pearson's chi-square test or independent t test. The KRG groups mean

scores decreased from 6.39 at baseline to 4.03 at week 8 ($p<0.001$) and the control group also decreased from 5.70 to 4.57, ($p=0.002$) which is not statistically significant ($p=0.391$). However, when adjusted using the Bonferroni correction the KRG group showed a greater decrease in inattention scores after 8 weeks than the control group showing that the difference was statistically significant with a medium effect size ($p=0.048$, Cohen's $d=0.47$). The hyperactivity scores at 8 weeks between the groups showed statistically significant difference ($p=0.019$) and when adjusted using the Bonferroni correction the difference is significantly greater in the KRG group when compared to the control group ($p=0.047$, Cohen's $d=0.49$) which is a medium effect size. Salivary cortisol and DHEA levels increased in both groups and significant between-group differences were not observed. The QEEG TBR decreased from 3.79 to 2.85 ($p=0.001$) in the KRG group and from 3.74 to 3.63 ($p=0.126$) in the control group. The Bonferroni adjustment showed that the KRG group had a significantly greater decrease in QEEG TBR with a large effect size ($p=0.001$, Cohen's $d=1.13$).

It was found that KRG extract significantly improved the inattention and hyperactivity/impulsivity symptoms and QEEG-TBR of the subjects and had a good safety profile; however, it did not have significant effects of cortisol and DHEA levels of chronically stressed children with ADHD symptoms. One KRG subject reported loose stool and two in the control group reported nausea unrelated to the placebo. The two groups did not differ significantly in terms of frequency of adverse events ($p=0.494$). The results suggest that KRG extract may be an effective and safe alternative treatment for children with inattention and hyperactivity/impulsivity symptoms.

Bos et al. (2015) conducted a 16-week, double-blind randomized, placebo-controlled trial to investigate whether dietary omega-3 fatty acid supplementation in boys with and without attention deficit/hyperactivity disorder would improve symptoms of inattention. Omega-3 PUFA is thought to play an important role in cognitive control.

A total of 40 boys aged 8-14 years of age with a DSM-IV diagnosis of ADHD were recruited through the University Medical Center in Utrecht, Netherlands, and through advertising. Only boys were chosen to limit potential confounds (such as gender) on brain activity. The children with ADHD were either not taking medications or using psychostimulant medication. A total of 39 typically developing boys matched to patient's age, hand preference, and body mass index were recruited as a reference group through advertising at schools in the area. All subjects were screened and none of the typically developing subjects were taking any form of psychoactive medication. Parents participated in a *Diagnostic Interview Schedule for Children-Parent Version* (DISC-P) interview to confirm the absence of any psychiatric condition and their first-degree relatives.

All subject's IQ were assessed using a short form of the *Wechsler Intelligence Scale for Children* (WISC-III). The children with ADHD had a slightly lower IQ score than the typically developing children. Hand preference was assessed using the *Edinburgh Handedness Inventory*. Cheek cell samples were assessed to measure phospholipid fatty acid (PUFA) levels and urine samples were collected to measure the HVA to creatinine ratio, as a proxy for dopamine turnover. The *Essential Fatty Acid Questionnaire* (EFAQ) was collected to assess symptoms of FA deficiency. The parent-rated *Child Behavior Checklist* (CBCL) and *Strengths and Weaknesses of ADHD symptoms and Normal behavior scale* (SWAN) were collected for all

participants, both of which measure the severity of ADHD symptoms. The CBLC (collected twice) was used as the primary outcome measure, whereas the SWAN (collected five times) was used to measure change over time. The *Teacher Report Form* (TRF) was sent out to classroom teachers at baseline and follow-up. The fMRI was performed SPM8 and scans were excluded if head motion exceeded 3mm. Thirteen children with ADHD and six typically developing children were excluded from the SPM fMRI analysis.

The 16-week trial followed a double-blind, randomized placebo-controlled design where investigators, parents, and participants were all blind to the treatment conditions. The 2x2 factorial design included four groups: children with ADHD receiving either placebo or omega-3 fortified margarine (ADHD-Placebo and ADHD-Active) and children from the reference group receiving the same treatment (RG-Placebo and RG-Active). All participants were instructed to consume a daily dose of 10 g of either normal or omega-3 fortified margarine. The active product was full fat (80%) margarine, containing 650 mg DHA and 650 mg EPA per 10 g serving. The placebo margarine contained monounsaturated fatty acids instead of EPA and DHA. Compliance was measured by weighing the leftover product that the parents returned on a monthly basis. Participants and parents kept a calendar to record when the margarine was consumed. They were asked to maintain their usual diet but to refrain from supplements containing omega-3 or foods fortified with EPA and DHA, nor were they to consume fatty fish more than once a week. Compliance was measured using the Diet and Lifestyle Change Questionnaire on monthly basis.

Behavioral and psychological measures were analyzed using independent samples t-tests or Mann-Whitney U-tests at baseline between the diagnostic groups, and between the

intervention groups. To investigate treatment effects, all variables of interest were analyzed using ANCOVA with the baseline measurement entered as a covariate.

ANCOVA showed a main effect of treatment condition where attention problems were greatly reduced after supplementation in comparison to the placebo group ($(F(1,67)=14.99, p,0.001)$). No significant effects were in rule breaking and aggressive behavior.

Supplementation of Omega-3 PUFA improved symptoms of inattention in both groups of boys, those with ADHD and those typically developing. At baseline, boys with ADHD had higher symptoms of inattention than boys that are typically developing. There was an effect of treatment on parent-rated symptoms of ADHD, regardless of diagnosis. This effect was driven by the measures of inattention at follow-up: subjects who had received the omega-3 PUFAs had lower scores on the CBCL attention problems subscale than subjects on the placebo. The results of this study indicate that typically developing children also benefit from omega-3 PUFA intake during development in general. Cheek cell phospholipids had increased levels of omega-3 PUFAs and DHA at follow-up for subjects treated with the active product than for those treated with the placebo. Subjects with ADHD with higher levels of DHA were associated with lower attention problems both at baseline and at follow-up. Limitations of this study include: cheek cell samples did not permit reliability detection of DHA; however, this did not affect the statistical analyses negatively; a small number of participants with ADHD had changes made to their medication during the intervention; however, when the subjects were excluded from analysis the effect of the intervention still held; sample sizes in the fMRI study were smaller than in the main study as a result of subject motion.

Table 1: Summary of Nutritional Supplements

AUTHORS	STUDY DESIGN	PARTICIPANTS	PROCEDURE	FINDINGS
Bilici, Yıldırım, Kandil, Bekaroğlu, Yıldırım, Değer, Ülgen, Yıldırım, & Aksu (2004)	Quantitative	400 children that met DSM-IV criteria for ADHD	12 weeks of double-blind treatment with Zinc Sulfate (150 mg/day) or placebo. Results were gathered through the use of the Attention Deficit Hyperactivity Disorder Scale (ADHDS), Conners Teacher Questionnaire, and DuPaul Parent Ratings of ADHD	Zinc sulfate was significantly superior to the placebo group in reducing hyperactivity, impulsive and impaired socialization symptoms, but not attention deficiency symptoms, as assessed by ADHDS, in older patients and in patients with high BMI score.
Konofal, Lecendreux, Keron, Marchand, Cortese, Zaïm, Mouren, & Arnulf (2008)	Quantitative	23 nonanemic children aged 5-8 years with serum ferritin levels <30 ng/mL and who also met DSM-IV criteria for ADHD	The children were randomized (3:1 ratio) to either oral iron or placebo for 12 weeks. The ADHD Rating Scale and the Conners' Parent and Teacher Rating Scales were used to measure symptoms.	Significant improvement in symptoms noted on all the rating scales for the individuals taking the iron supplement but not for the placebo group. May be a beneficial intervention if children have low serum ferritin levels.
Gustafsson, Birberg-Thornberg, Duchén, Landgren, Malmberg, Pelling, Strandvik, & Karlsson (2010)	Quantitative	92 children aged 7-12 that met DSM-IV criteria for ADHD combined type	Children were administered PlusEPA (500 mg + 2.7 mg DHA and 10 mg Vitamin E) or an identical placebo of rapeseed oil for 15 weeks. Conners' Parent/Teacher Rating Scale, ADHD-RS, Raven's Progressive Matrices, Qb-test and serum and blood levels.	Significant reduction of ADHD symptoms was reported in the EPA group. Inattention/cognitive in the classroom was improved for the teacher rating. Children responding to the treatment initially had low levels of EPA.

Table 1 (continued)

AUTHORS	STUDY DESIGN	PARTICIPANTS	PROCEDURE	FINDINGS
Lee, Lim, & Park (2011)	Quantitative	18 subjects aged 6-14 that met DSM-IV criteria for ADHD	KRG (1000 mg twice daily) was administered for 8 weeks and efficacy was measured using ADS, CPRS, CTRS, DuPaul ADHD Rating Scales, Kovac's CDI, SAIC, TAIC, K-CBCL, and KPI-C.	The KRG treatment showed improvement in inattentiveness in children with ADHD but not the general severity of ADHD, depression, anxiety personality and behavioral changes.
Ko, Kim, Kim, Moon, Whang, Lee, & Jung (2014)	Quantitative	70 subjects aged 6-15 that had six or more symptoms of inattention or hyperactivity/impulsivity from DSM-IV for ADHD as well as ADHD NOS	Subjects were administered a pouch containing 40 mL of KRG or identical placebo twice daily for 8 weeks. Inattention and hyperactivity/impulsiveness scale questionnaire, saliva samples, and QEEG used to measure the efficacy of the KRG treatment.	Inattention and hyperactivity/impulsiveness scores showed a significant improvement in the treatment group when compared to the control group. There were no significant differences between groups for Salivary cortisol and DHEA levels. The KRG group showed a significantly greater decrease in their QEEG TBR.

Table 1 (continued)

AUTHORS	STUDY DESIGN	PARTICIPANTS	PROCEDURE	FINDINGS
Bos et al. (2015)	Quantitative	40 boys aged 8-14 that meet DSM-IV criteria for ADHD. 39 typically developing boys were included as a reference group. Participants included both, not taking medication and taking psychostimulant medication.	Only boys were included to reduce potential confounds on brain activity. Participants received a daily dose of either placebo 10 g or omega-3 fortified margarine 10 g (containing 650 mg DHA and 650 mg EPA) for 16 weeks. All participants, investigators and parents were blind. Fatty acid levels were checked by cheek swab and EFAQ. CBCL, SWAN, TRF, and fMRI were used to evaluate efficacy.	Symptoms of inattention were improved in both the boys with ADHD and the boys typically developing. It was found to improve inattention more specifically than general ADHD symptoms. Cheek cells showed higher levels of DHA at the end of the study. Subjects with ADHD with higher levels of DHA were associated with lower attention problems.

Food Additives

Artificial food colors and other food additives (AFCA) have long been suggested to affect behavior in children. Known effects of AFCA is producing overactive, impulsive, and inattentive behavior, or hyperactivity. Children that exhibit this pattern of behavior to a large degree are probably diagnosed with ADHD (McCann et al., 2007). Two studies have been included in this section.

Bateman et al. (2004) studied the effects of a double blind, placebo controlled, artificial food colorings, and benzoate preservative influence on hyperactivity in a general population

sample of preschool children. The authors hypothesize that food additives have a pharmacological effect on behavior regardless of other characteristics of the child.

Two hundred seventy-seven children were selected for the 4-week study. The children were 3 years old and underwent screening of behavior using the *Weiss-Werry-Peters Activity Scale* (WWP) and the *Behavior Checklist* (BCL) to measure hyperactivity and skin prick testing for reactivity to common allergens: dust mites, grass pollen, cat, milk, egg, and peanut. Following the screening the children were divided into four groups for a randomized, double-blind, placebo-controlled, crossover study. The groups were hyperactive and atopic, non-hyperactive but atopic, hyperactive but not atopic, and non-hyperactive and nonatopic. The 4-week study consisted of the children following an artificial coloring and a sodium benzoate free diet. On weeks 2 and 4 the children consumed daily a juice containing 300 mL of mixed fruit juices (placebo or active) in identical bottles. The active drink contained 20 mg of artificial food colors (sunset yellow, tartrazine, carmoisine, and ponceau 4R; 5 mg of each) and 45 mg of sodium benzoate. Each week research psychologists assessed the children's behavior during free periods and structured tasks to measure inattention, activity, and impulsivity.

ANOVA analysis and repeated measures analysis of variance were used to measure effects of the challenges. The effect of food additives and colorings on hyperactivity for the parent rating was substantial. The parent rating of hyperactivity while on the placebo was 0.38 and for the active supplement was 0.77. The difference of 0.39 between the 2 changes is 0.39 and represents an effect size of 0.51. The removal of food additives and colorings from the diet had a beneficial effect as measured by parents but not by clinical assessments. No significant changes in tests scores for either the active or placebo periods were seen by clinical measures;

however, parental ratings showed significant changes between the active and placebo periods. During the active period they indicated a significant increase in hyperactivity behavior, as well as aggregate parental hyperactivity rating but not for impulsivity and inattention. A limitation of the study is that the parents of the children participating in the study could not be blinded to the removal of food additives and colorings.

McCann et al. (2007) investigated the effects of food additives on hyperactive behavior in 3-year-old and 8/9-year-old children by designing a community based, double-blinded, placebo-controlled food challenge to determine whether the effects could be seen with a broad range of measures of hyperactivity.

Participants for the study were recruited from early-years settings for the children aged 3 years to 4 years, 2 months (n=153, boys=79, girls=74) and from children aged 8 and 9 (n=144, boys=75, girls=69) attending schools in Southampton, UK. The sample study includes children from a full range of socioeconomic backgrounds. Participating schools and early-childhood settings received contributions towards school funds.

The study design and protocols for age groups are similar and consisted of a within-subject crossover between two active mixes (A and B) and a placebo drink. For the 3-year-old group, mix A consisted of 20 mg of artificial food colorings (5 mg sunset yellow, 2.5 mg carmoisine, 7.5 mg tartrazine, and 5 mg of ponceau 4R) and 45 mg of sodium benzoate. Mix B included 30 mg of artificial food colorings (7.5 mg sunset yellow, 7.5 mg carmoising, 7.5 mg quinoline yellow, and 7.5 mg allura red AC) and 45 mg sodium benzoate. The amounts in the mixes were multiplied by 1.25 for the 8/9-year-old group. Mix A contained 24.98 mg of artificial food colorings (6.25 mg sunset yellow, 3.12 mg carmoisine, 9.36 mg tartrazine, and

6.25 mg of ponceau 4R) and 45 mg of sodium benzoate. Mix B included 62.4 mg of artificial food colorings (15.6 mg sunset yellow, 15.6 mg carmoisine, 15.6 mg quinoline yellow, and 15.6 mg allura red AC) and 45 mg sodium benzoate. Dosages of the mixes A and B administered to the 3-year-old group were roughly the same as the amount of food coloring in two 56g bags of sweets. For the 8/9-year-old group, mix A was equal to about two bags of sweets and mix B was equal to about four bags of sweets a day.

Baseline data were gathered after a week on their typical diet at week 0 and then artificial colors and sodium benzoate that was to be used in the study were withdrawn from their diet for the 6 weeks of the study. Week 1: withdrawal period but receiving placebo; weeks 2, 4, and 6: challenge with random assignment to two active periods and one placebo period; weeks 3 and 5: washout continuing placebo. During this period, the 3-year-old group received the challenge and washout-placebo drink on a weekly basis and consumed mixed fruit juices (placebo or active) at home (300 mL/day for 3-year-old children, 625 mL/day for 8/9-year-old children).

All the preparation and packaging of juice drinks were done by administration and delivered to homes every week by the blinded research team and questionnaires and other forms were obtained and dispensed. Parents recorded juice consumption and compliance daily.

Three measures of behavior were used to calculate *Global Hyperactivity Aggregate* (GHA) for 3-year-old with an additional measure for the 8/9-year-old group. The teacher version of an abbreviated ADHD rating scale IV, an abbreviated version of the *Weiss-Werry-Peters* (WWP) hyperactivity scale was completed by parents and a parent version of an abbreviated ADHD rating scale IV was used with the 8/9-year-old group, and classroom or early

childhood setting observations were used to evaluate all the participants. A fourth measure for the 8/9-year-old group was the *Conners Continuous Performance Test II* (CPTII).

The age groups were measured and treated as independent parallel studies. Linear mixed-model methods were used to analyze data: Model 1 measured the fixed effect testing for mix A against placebo and mix B against placebo. Model 2 adjusted the effects of the following factors: week during study, sex, GHA in baseline week, number of additives in pretrial diet, maternal education level, and social class. A compound symmetry covariance matrix was the best-fit for measuring the 3-year-old group and an unstructured covariance matrix was used for the 8/9-year-old group.

Of the 153 3-year-old participants, 117 had complete GHA data, many of them did not consume all the drinks required. Model 1, the results on all three samples had significant adverse effects of mix A on GHA compared to the placebo but the high GHA scores for mix B were not significantly greater than for the placebo. For Model 2, the effect of mix A was significant for the entire sample ($p=0.044$), by contrast with that of mix B ($p=0.093$). When analyses are restricted to those children that consumed at least 85% of the juice ($n=103$), the adverse effect of mix A was still significant ($p=0.016$), but not significant for mix B ($p=0.098$). The complete case groups showed the same pattern of results (mix A, $p=0.020$; mix B, $p=0.131$).

Of the 144 8/9-year-old participants, 114 had full GHA data during active and placebo weeks. For Model 1 the effects of mix A and mix B were significantly greater than that of the placebo, with the exception of the entire sample in which the effects of mix A versus the placebo fail to reach significance. Model 2, the effect of mix A for the entire sample was not significant ($p=0.123$) but mix B did have a significantly adverse effect compared with the placebo

($p=0.012$). When analyses are restricted to those children that consumed at least 85% of the juice ($n=98$), the adverse effect of mix A remained non-significant ($p=0.066$), but was significant for mix B ($p=0.003$). The complete case groups showed higher GHA scores than the placebo for mix A ($p=0.023$) and mix B ($p=0.001$).

This study has found the effects of a mix of additives commonly found in children's food increases the mean level of hyperactivity in children aged 3 years and 8/9 years old and provides evidence of adverse effects of AFCA on children's behavior. The findings of this study are seen not only in children with extreme hyperactivity (ADHD) but in the general population and across the range of severities of hyperactivity.

Table 2: Summary of Food Additives

AUTHORS	STUDY DESIGN	PARTICIPANTS	PROCEDURE	FINDINGS
Bateman et al. (2004)	Quantitative	277 3-year-old children	Child followed an artificial coloring and sodium benzoate free diet. Weeks 2 and 4 the children consumed a juice containing 300 mL of mixed fruit juices (placebo or active). The active drink contained 20 mg of artificial food colors and 45 mg of sodium benzoate. Children were evaluated weekly.	Significant reductions of hyperactivity during the withdrawal periods and significant increases of hyperactivity behavior during the active period vs. placebo on parent ratings. Clinical ratings showed no significant difference.

Table 2 (continued)

AUTHORS	STUDY DESIGN	PARTICIPANTS	PROCEDURE	FINDINGS
McCann et al. (2007)	Quantitative	137 3-year-old participants 130 8/9-year-old participants	Two active mixes containing different quantities of artificial colorings and additives commonly found in children's foods (A and B) and a placebo drink. The Weiss-Werry-Peters hyperactivity scale, classroom observation code, and Conners Continuous Performance test II was used as a measure for the 8/9 year olds.	When the 3-year-old children consumed the mix A they saw significant adverse effects compared to the placebo but not in mix B. The 8/9-year-old group displayed significant adverse effects after consuming both mix A and mix B compared to the placebo.

Restricted Elimination Diet

The elimination diet, also known as the restricted elimination diet (RED), for the following studies is based on a few foods diet. The idea behind the few foods diet is that children might demonstrate ADHD symptoms after eating certain foods. The diet consists of a limited number of hypoallergenic foods such as: rice, turkey, lamb, a range of vegetables (lettuce, carrots, cauliflower, cabbage and beet), pears, and water. No other foods were allowed but the foods from the few foods diet were allowed every day in normal doses. Non-dairy calcium was supplemented daily. Complementary foods such as: potatoes, fruits, corn and wheat were allowed on days and in doses outlined in advance according to an intake schedule.

Pelsser et al. (2009) conducted a randomized controlled trial into the effects of food on ADHD to assess the efficacy of a restricted elimination diet in reducing symptoms in children.

Seventy-nine Dutch children were referred to the ADHD Research Center and 27 were selected to participate in the study. They were aged 3.8-8.5 years old and met DSM-IV criteria for Combined Type or Hyperactivity-Impulsive Type. Exclusion criteria included: adopted or foster children, coexisting neurological disease, an IQ below 70, prematurity or dysmaturity, use of alcohol or smoking by mother during pregnancy, and coexistence of other psychiatric disorders, except for oppositional defiant disorder (ODD) and conduct disorder (CD). None of the children used psychotropic medication.

Primary outcomes were measured using parent and teacher ratings on the *Abbreviated 10-item Conners Scale* (ACS) and the *ADHD Rating Scale* (ARS) before and after the elimination diet. Secondary outcomes were measured using parent ratings on ODD symptoms measured by a *Structured Psychiatric Interview* (SPI). The parents and teachers who filled in the questionnaires were not blinded as they had to supervise the food intake.

Data were analyzed on an intention-to-treat basis, effect size were % scale reduction and Cohen's *d*. Effects were tested at $p=0.05$; all testing was two-tailed. Data were analyzed by Student's *t* test and Fisher's exact test.

Results for after the trial revealed that the intervention group showed a 62.6% improvement on the ACS and a 70.3% improvement on the ARS ($p<0.001$). The children in the intervention group also demonstrated significantly decreased behavior problems in comparison children in the control group. The treatment of effect of the ARS for inattention between the intervention and control group (mean difference 11.8, $p<0.001$) and hyperactivity//impulsivity (mean difference 14.1, $p<0.001$). The parent rating showed that 11/13 children in the intervention group showed an improvement of 50% or more and none of the children in the

control showed an improvement of 50% or more. Teacher measures also show a significant difference between intervention and the control group for inattention (mean difference 8.3, $p<0.011$) and hyperactivity/impulsivity (mean difference 12.8, $p<0.002$).

Restricting and carefully supervising foods in children has shown significant improvement in behavior. It was noted that responders (parent rating, 11 out of 15, 73%) (teacher rating, 7 out of 10, 70%) of the intervention group no longer met the DSM-IV criteria for ADHD. Eighty percent of the children in the intervention group also met the criteria for ODD and 83% in the control group. Following the intervention, the number of children that met the criteria for ODD was reduced by 66% for the intervention group but no effect was shown for ODD in the control group. Limitations include: no placebo and parents and teachers were not blinded to the intervention.

Pelsser, Frankena, Buitelaar, and Rommelse, (2010) studied the effects of food on physical and sleep complaints in children with ADHD. They conducted a randomized controlled pilot study to: 1) examine whether the physical and sleep complaints could be resolved using an elimination diet; 2) investigate whether the effect of a diet on physical and sleep complaints was limited to children that had improvements in behavior on a RED; and 3) investigate whether effects of an RED on physical and sleep complaints was limited to children with an allergy.

Twenty-four children completed the study after meeting the inclusion criteria of being aged 3-8 years old; met DSM-IV criteria for ADHD combined type or hyperactive-impulsive type, behavior problems were evident before age 4, and not on medication. Exclusions include: diagnosed with autism spectrum disorder, pre- or dysmature at birth, or maternal smoking during

pregnancy. The participating children were randomly assigned to the diet group (n=13) or the control group (n=11).

Physical and sleep complaints were measured by *Physical Complaints Questionnaire* (PCQ) that was completed by parents once after baseline and again when the study ended. The physical complaints measured by the assessment include: 1) pain (headaches, abdominal pains and growing pains), 2) unusual thirst or perspiration, 3) eczema, 4) asthma or persisting cold (rhinitis), 5) skin problems (blotches in the face, red ears, red-edged mouth or bags under the eyes, 6) tiredness, and 7) gastrointestinal problems (diarrhea, constipation and flatulence).

After random assignment, all the participants started a 2-week baseline diet or eating as normal; no foods were eliminated. Parents kept a journal of their child's diet, behavior, physical complaints, sleep complaints, and activities. Following the baseline period, children in the diet group began their diet consisting of foods included in the few foods diet with complementary foods allowed as allocated on the schedule for 5 weeks. If no improvements were noted by the end of week 2, diets were restricted further to only the few foods diet. The control group continued their normal diet so that no foods were excluded for 5 weeks.

Differences in averages within groups of the parent ratings on the PCQ before and after the trial were tested by Student's *t* test and expressed by Cohen's *d*. Differences in presence or absence of complaints between the groups are presented in terms of odds ratio (OR) and their *p* values. Following the trial, all the children (n=11) in the control also completed the RED.

Secondary endpoints analyzed using linear and exact logistic regression and calculated in all 24 children who completed the diet. Responders, refer to the children that showed a reduction in ADHD symptoms of 50% or more following the diet and non-responders, refer to the children

that showed less than 50% reduction of ADHD symptoms while on the diet. Spearman rank correlation coefficients were calculated to evaluate the physical complaints and ADHD symptoms after following the diet.

The total number of complaints at the start of the trial was 44 and was reduced to 10 complaints at the end for the diet group. This is a reduction of 77% ($p < 0.001$) with an effect size of 2.0. The control had 36 complaints at the start of the trial and 30 at the end showing a reduction of 17% ($p < 0.08$) with an effect size of 0.2. The OR scores of the presence/absence of symptoms for three domains are: 1) headaches or bellyaches (OR=13.25), 2) unusual thirst or unusual perspiration (OR=10.04), and 3) sleep complaints (OR=11.77). The complaints were significantly reduced in the diet group and less so in the control group ($p < 0.05$). Responders, 20 of 24, showed an average reduction of 69.4% on the ARS (effect size 2.1) parent ratings there was reduction of 70.6% (effect size, 2.5) for teacher ratings. The responder group showed a significant reduction of physical complaints ($p < 0.001$); the non-responder group, the reduction was not significant ($p = .35$), with effect sizes of 1.4 and 0.8. Spearman's rho was 0.54 ($p < 0.01$), indicating there was a positive correlation between the reduction of physical and behavioral symptoms. The reduction of physical complaints for atopic children as well as non-atopic children was significantly reduced after the diet.

It is common for children with ADHD to also have physical complaints such as headache, bellyache, tiredness, eczema, and sleep complaints. In this study, the intervention significantly reduced the ADHD symptoms. The report that the results indicate that comorbidity between ADHD and physical complaints is high. Limitations of the study include: the diet is very restricted and difficult to create a comparable placebo, parents could not be blinded to the

intervention, parents had to pay more attention to their children which, in turn, could improve behavior and somatic complaints, sample size is small, and short in time.

In *The Impact of Nutrition on Children with ADHD* (INCA) Pelsser et al. (2011) investigated the effects of a restricted elimination diet on the behavior of children with attention-deficit hyperactivity disorder. The authors conducted a 13-week, randomized, controlled trial to test whether ADHD is triggered by foods and to differentiate between non-allergic and allergic mechanisms in food induced ADHD.

Participants were recruited from medical centers and through media in the Netherlands and Belgium. Inclusion criteria of having diagnosis of ADHD of any subtype, aged 4-8 years old, and parents with adequate knowledge of Dutch and who were motivated to follow a 5-week restricted elimination diet (RED) was required. Exclusion criteria were children receiving drugs or behavior therapy for ADHD, children already following a diet, or family circumstances that were likely to prevent completion of the study.

Four questionnaires were used to collect data: the ARS which measured inattention, hyperactivity and impulsivity; the ACS measures hyperactivity, impulsivity, attention, mood, and temper tantrums; *Strengths and Difficulties Questionnaire* (SDQ) which measured emotional symptoms, conduct, hyperactivity-inattention, and peer problems; and SPI was used to assess ODD and conduct disorder. Unblinded parent and teacher assessments (ACS, ARS, and SPI) and blinded pediatrician assessments (ARS and SPI) were conducted to establish baseline and again at the end of the first phase. Blood samples were taken at the start and the end of the first phase to evaluate IgE (chicken egg, peanut, soy, milk, fish, and wheat) and IgG (270 different

foods) levels using ImuPro test. Each analyzed food was categorized as being a low IgG food or a high IgG food.

Following baseline assessments, the children were randomly assigned to the diet group or the control group and began a 2-week baseline period of not excluding any foods from children's diet. Parents recorded information on diet, behavior, activities, physical complaints, and medications in a journal. The ACS and ARS (parents) and the SDQ (parents and teachers) assessments were completed again upon completion of the baseline period. The start of the first phase began at week 4, the diet group started a 5-week RED that consisted of the few foods diet (rice, meat, vegetables, pears, and water). Potatoes, fruits, and wheat were allowed to make the intervention easier for parents and children; however, if no changes in behavior were reported, the diet was restricted to only the foods in the few foods diet. At the end of the first phase, assessments were completed and blood samples taken. Participants that had behavior improvements of 40% or better on the ARS entered the challenge phase and non-responders left the trial.

During the second phase (double-blind crossover challenge phase, weeks 10-13) the control group continued as it did in the first phase and the responders from the diet group were randomized to two food groups (those eating low IgG foods and those eating high IgG foods), adding foods from the low IgG or high IgG while continuing the RED based on each child's IgG levels. Three foods from 270 different foods were added to each child's diet consecutively for 2 weeks and managed by a dietician. All behavioral measurements were double-blind and all children were to complete both challenges. Parent ACS and ARS assessments were completed after each challenge; other assessments were completed at weeks 11 and 13 if there was a relapse

in behavior. If no-relapse was reported in the ARS the child continued on to the next challenge. Blood samples were collected following a relapse in behavior or at week 13 if no-relapse was reported.

The ARS and the SPI measurements were calculated kappa values and intra-cluster correlation coefficients (ICC). Kappa values greater than 0.75 (ICC>0.80) were taken to represent excellent agreement; values below 0.40 (ICC<0.40) suggests poor agreement. Behavior endpoints were assessed using GLM with treatment (diet group vs. control group) block, and interactions and baseline scores as covariates. The correlation between clinical response and treatment, and its association with IgE levels was calculated using Fisher's exact test. The crossover challengers were measured with the Mainland-Gart procedure and the Prescott test.

From the first phase, 78% of the diet group responded positively with ARS scores (blinded pediatrician and unblinded teacher) were significantly lower at the end of the first phase than at baseline in comparison to the control group. Both kappa and ICC scores on the ARS and SPI for parent and pediatrician the agreement was greater than 0.40 (mean 0.90) for ICC and 0.83 for kappa. ACS scores were also significantly lower in the diet group in comparison to the control group for both parent ($p<0.0001$) and teacher ($p<0.0001$). Thirty of 32 responders proceeded on to the challenge phase and 19 of the participants showed a relapse after one or both challenges. The decrease in the ARS score from baseline to the end of the first phase was 35.9 (95% CI 33.2-38.6; $p<0.0001$) which increased after the challenge by 20.8. The decrease in the ACS score from baseline to the end of the first phase was 18.3 (95% CI 16.7-19.9; $p<0.0001$) which increased after the challenge by 11.6. The control group's ARS and ACS score did not

differ between baseline and the end of the first phase. Twenty-nine of the 30 responders were included in the IgG assessments. Eleven were assigned to the low-IgG foods challenge and 18 to the high-IgG foods challenge. Each challenge was followed by the other challenge. Thirteen of 29 low-IgG and 13 of IgG challenges had a relapse of ADHD behavior. No relapse was reported in 11 of 29. The order of the challenges was not significantly associated with reported relapse (Mainland-Gart $p=1.0$, Prescott $p=0.38$). The IgG type showed no significant effects of high vs. low.

The RED had significant positive effect on ADHD symptoms in 64% of the children participating in the diet group, and reintroducing foods led to a significant relapse in ADHD behavior. IgG blood levels for specific foods did not predict which foods might affect behavior. Limitations of the study include: parents and teachers were not blinded to the study. The clinical assessment for the control group was completed at week 13 and the diet group was assessed at week 9 which could have revealed to the pediatrician who was participating in the diet group and control group. Behavior improvements in the first phase could have been the result of increased attention in the diet group. To avoid this the control group received education on healthy foods and both groups of parents kept journals of their child's participation.

Pelsser, van Steijn, Frankena, Toorman, Buitelaar, and Rommelse, (2013) conducted a randomized controlled pilot study into the effects of a restricted elimination diet on family structure in families with ADHD and ODD and whether behavior improvements in the RED trials are the result of a difference in parenting structure rather than the diet changes.

A subsample of 24 participants (ADHD RED group $n=11$) (ADHD control group $n=13$) from the INCA study took part in this pilot study. Inclusion and exclusion criteria for the INCA

study were used for selection of participants. A control group (n=23) was recruited through teachers participating in the INCA study children without ADHD aged 4-8.

The Dutch version of the *Family Environment Scale* (FES) to measure family relationships and structure. The FES consists of 77 yes/no questions and 7 subscales: 1) cohesion (family commitment and support), 2) expressiveness (expression of feelings), 3) conflict (expression of anger and aggression), 4) organization (structure and planning of family life), 5) control (rules used in a family life), 6) family values (opinion about norms and behavior), and 7) social orientation (involvement in the social environment). The 18-item *ADHD DSM-IV Rating Scale* (ARS) to assess ADHD and a semi-structured DSM-IV-based, psychiatric interview was used as measures in the study. Two index scores were used in this study: the family relationships index (FRI), based on three subscales (cohesion, expressiveness, and conflict) and family structure index (FSI), based on two subscales (organization and control).

The study gathered data at baseline and at the end of the trial in both ADHD groups and the non-ADHD control group. Participants in the ADHD group were randomly assigned to the RED group or the ADHD control group. While the RED group followed the few foods diet consisting of rice, meat, vegetables, pears, and water they were also allowed to supplement with potatoes, fruits, and wheat to create a less restrictive diet that would be easier to follow for the children and their parents. If no behavior changes were reported the diet was restricted to the few foods only. The ADHD control group received healthy food advice and the non-ADHD group received no intervention. Parents in all groups completed the FES and a blinded pediatrician for both the ADHD groups evaluated the ADHD and ODD behavior ratings.

The difference between groups values at baseline were obtained using the general linear model (GLM) and Cohen's *d* was calculated as effect size estimate. *P*-values were obtained by the Welch-Satterthwaite equation. FES outcomes at the end of the study were obtained using the GLM. ADHD and ODD were analyses were by intention-to-treat and based on blinded measurements. Repeated measurement models were used to separately analyze the moderating role of relationship and structure.

FRI and FSI scores at baseline for the ADHD group and the non-ADHD group were similar. Both ADHD groups had higher scores on the conflict subscale than the no-ADHD group. The effects of RED on ADHD score showed that FRI was significantly associated with the ADHD score and an inverse relationship between the number of ADHD symptoms and the family relationship: higher ADHD score, the lower the FES Relationships Index score. There was no effect of FSI on ADHD found and changes in both FRI and FSI did not mediate or moderate the results of the RED on ADHD symptoms. Similar results were found for ODD.

The findings of the study indicate that: 1) the family environment of children with ADHD, motivated to follow a 5-week RED, is similar to the family environment of non-ADHD and found to be better than norm; 2) family relationship and structure were not affected by the 5-week RED; 3) the effects of RED on symptoms of ADHD and ODD are not mediated by changes in family relationships and structure; and 4) family relationships but not structure were inversely associated with ADHD and ODD. Limitations of the study are that parents knew well in advance the strict expectations of the diet. Parents who would possibly have a hard time following the diet would have chosen to not participate and parents who were confident of their

parenting capabilities would be more likely to participate. The sample that participated in the study may have had above average family environments.

Table 3: Summary of Restricted Elimination Diet

AUTHORS	STUDY DESIGN	PARTICIPANTS	PROCEDURE	FINDINGS
Pelsser, Frankena, Toorman, Savelkoul, Pereira, & Buitelaar (2009)	Quantitative	27 children aged 3.8-8.5 years that met the DSM-IV criteria for ADHD Combined Type or Predominantly Inattentive Type	3 measures were taken during a 5-week few foods diet that limited to few hypoallergenic foods. Journals of observations, abbreviated ten-item Conners Scale (ACS) and the ADHD Rating Scale (ARS).	Following the trial period the intervention group showed a 62.6% improvement on the ACS and a 70.3% improvement on the ARS. The control group ACS score increases 4.4% and decreased ARS by 2.2%.
Pelsser, Frankena, Buitelaar, & Rommelse (2010)	Quantitative	24 children aged 3-8 that met the DSM-IV criteria for ADHD Combined Type or Predominantly Hyperactive-Impulsive Type	The children participating followed an elimination diet that consisted of limited foods from the few foods diet and a control group for 5 weeks. Assessments included Physical Complaints Questionnaire (PCQ).	Following the elimination diet, children showed a symptom reduction of 77%. Parents had to provide extensive journaling of observations and symptoms. This special attention could have positive results affecting the number of complaints.

Table 3 (continued)

AUTHORS	STUDY DESIGN	PARTICIPANTS	PROCEDURE	FINDINGS
Pelsser, Frankena, Toorman, Savelkoul, Dubois, Pereira, Haagen, Rommelse, & Buitelaar (2011)	Quantitative	100 children aged 4-8 years were selected to participate in the Impact of Nutrition on Children with ADHD (INCA) study. Children met DSM-IV criteria for ADHD any subtype.	The study restricted foods to the few foods diet for 5-weeks and used blood tests to test for allergies and sensitivities to foods. The children were assessed using ADHD Rating Scale (ARS), Standard Psychiatric Interview (SPI), Abbreviated Conners' Scale (ACS) and the Strengths and Difficulties Questionnaire (SQQ).	<p>Blood tests did not reveal food allergies but possible food sensitivities in elevated IgE levels in a few children.</p> <p>The controls groups ARS and ACS scores did not change across the trial.</p> <p>The diet groups ARS (blind pediatrician rated) and ACS (parent-rated) scores significantly decreased from baseline.</p>
Pelsser, van Steijn, Frankena, Toorman, Buitelaar, & Rommelse (2013)	Quantitative	24 children aged 4-8 that met DSM-IV criteria for ADHD that were selected to participate in the INCA study. The study included a control group of 23 without an ADHD diagnosis aged 4-8 years.	<p>Children were randomly assigned to either a 5-week restricted elimination diet (RED) (n-11) or a control group (n-13) that received healthy food advice. The effects on the family environment were assessed.</p> <p>The families were given a pre and post Family Environment Scale (FES) assessment.</p>	<p>Families likely to participate in a RED are likely to be similar to the families of the children without ADHD and may have consisted of above average family environment.</p> <p>Family relationships and the structure were not affected by following the RED.</p>

Chapter 3: Conclusions and Recommendations

The purpose of this research paper was to evaluate the effectiveness of nutritional interventions for treating symptoms of ADHD. Chapter 1 provided background information on the topic, and Chapter 2 presented a review of the research literature. In this chapter, I discuss findings, recommendations, and implications from research findings.

I reviewed 12 studies that investigate nutritional supplements to reduce symptoms of ADHD and the association between foods and additives and symptoms of ADHD in children. Six of the 12 studies used supplementation (Bilici et al. 2004; Bos et al., 2015; Gustafsson et al., 2010; Ko et al., 2014; Konofal, et al., 2008; Lee et al., 2011). Two studies investigated the effects of artificial food additives and food colorings (Bateman et al., 2004; McCann et al; 2007). Four studies examined the effects of a restricted/elimination diet (Pelsser et al., 2009; Pelsser et al., 2010; Pelsser et al., 2011; Pelsser et al., 2013).

Six of the 12 studies used supplementation: one study evaluated the effects of zinc sulfate (Bilici et al., 2004); one study used an iron supplement (Konofal et al., 2008); two studied fatty acids (Bos et al., 2015; Gustafsson et al., 2010), and two studied Korean red ginseng (Ko et al., 2014; Lee et al., 2011)

Four of the 12 studies investigated the effects of a restricted/elimination diet. Two studied the effects of the diet on symptoms of ADHD (Pelsser et al., 2009; Pelsser et al., 2011), one study assessed the effects of the diet on physical and sleep complaints (Pelsser et al., 2010), and one study investigated the effects of the diet on family structure (Pelsser et al., 2013).

Supplementation of Fatty Acids. The two studies on the effects of fatty acid supplementation for improving symptoms of ADHD showed remarkable improvements for the

participating children. One study examined the effects of EPA and reported a significant improvement in inattention/cognitive symptoms (Gustafsson et al., 2010). Bos et al. (2015) reported that children with ADHD with higher levels of DHA were associated with lower attention problems at baseline and at follow-up. In both the Gustafsson et al. (2010) and Bos et al. (2015) studies, children with lower levels of PUFA at baseline were the ones to benefit the most. This pattern of improvement with increasing levels of fatty acid suggests that children with ADHD might benefit from fatty acid supplementation.

Supplementation of Vitamins and Minerals. Two studies evaluated the effects of vitamin and mineral supplements on the symptoms of children with ADHD. Bilici et al. (2004) examined the effects of zinc sulfate and reported that significant improvements were evident at week 4 and maintained through week 12 with hyperactivity, impulsivity, and impaired socialization. Konofal et al. (2008) studied the effects of iron supplementation and suggested that a deficiency could be contributing to symptoms of ADHD. Symptoms on the rating scales were significantly reduced after 12 weeks.

Herbal Supplementation. The two studies on Korean red ginseng showed remarkable improvements for the children participating. In both the Lee et al. (2011) and Ko et al. (2014) studies, a significant difference was found in inattention and hyperactivity/impulsivity symptoms. The results suggest that KRG extract may be an effective and safe alternative treatment for inattention and hyperactivity symptoms.

Food Additives and Colors. Two studies that examined artificial food additives and food colorings commonly found in children's food. Bateman et al. (2004) and McCann et al. (2007) found that hyperactivity behaviors increased significantly when the children consumed the

mixtures containing artificial food colors and sodium benzoate. The findings of the two studies provide evidence of effectiveness that limiting or removing artificial food colorings and sodium benzoate might benefit children with symptoms of hyperactivity.

Diets. Three studies examined the effects of limiting foods and following a restricted diet on symptoms of ADHD such as behavior, physical, and sleep complaints. Pelsser et al. (2009) found that restricting and carefully supervising foods in children significantly improved behavior in the participants so much so the majority of the participants no longer met the DSM-IV criteria for ADHD. Pelsser et al. (2010) only measured the effects of a RED diet on physical and sleep complaints and found a reduction of 77% for total complaints in the diet group. Pelsser et al. (2011) found that the RED had a significant positive effect on ADHD symptoms in 64% of the participants in the diet group, and reintroducing foods led to significant relapse in ADHD behavior. IgG levels for specific foods did not predict which foods might affect behavior. Pelsser et al. (2013) investigated the effects of the diet on family structure and found the environment of families motivated to participate in a restricted diet are above norm, relationships and structure were not affected, the effects of the diet on symptoms were not due to changes in family relationships and structure, and family relationships but not structure were inversely associated with ADHD.

Recommendations for Future Research

In this section of the review of literature, recommendations for future research based upon limitations of the studies in Chapter 2 are discussed. Overall, small sample sizes were problematic in most of the studies, and some did not compare findings to a placebo or control

group. More studies need to be conducted to evaluate the efficacy of nutritional treatments over a longer intervention period in order to evaluate long-term effectiveness.

With regard to the diet studies, a common limitation noted was that it was not possible to blind the parents and teachers, as they were required to prepare food for the participants.

Another limitation was whether parents willing to participate in a diet study with strict expectations would be more confident in their parenting capabilities and have above average family environments.

Implications for Current Practice

The topic of non-medical treatment is very controversial. Families may choose non-medical treatment options in a desperate search for interventions that will alleviate their child's symptoms without putting their health and personalities at risk. ADHD is one of the most common behavioral disorders that continue into adulthood and at this point researchers speculate that nutrition plays an important role in symptoms.

To date, it has been most commonly treated with psychostimulant drugs and behavior therapy. However, it is critical that providers research, identify, and work with parents to find treatment solutions that are effective in treating ADHD and will do more good than harm. Thus, I will continue to advocate for alternative treatment options to prescribing medications to children with ADHD.

Summary

The findings of these studies were promising, in that symptoms of ADHD could be managed by certain supplements, avoiding artificial food additives and colorings, and/or by restricting foods. Non-medical treatment of ADHD is not new and is sought out in an effort to

avoid the negative side effects of prescription medications. The treatment of ADHD should not be considered a one size fits all approach. Exploring alternative options is critical when considering each child's unique needs.

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